DRAFT (7-16-02)
NTP-CERHR Report on the Potential Human Reproductive and Developmental Effects of Di-*n*-Butyl Phthalate (DBP)

Preface

The National Toxicology Program (NTP) established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in 1998. The CERHR is a publicly accessible resource for information about adverse reproductive and/or developmental health effects associated with exposure to environmental and/or occupational chemicals. The CERHR is located at the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health and Dr. Michael Shelby is the director.[1]

The CERHR broadly solicits nominations of chemicals for evaluation from the public and private sectors. The CERHR follows a formal process for review and evaluation of nominated chemicals that includes multiple opportunities for public comment. Chemicals are selected for evaluation based upon several factors including the following:

- potential for human exposure from use and occurrence in the environment.
- extent of public concern.
- production volume.
- availability of scientific evidence for reproductive and/or developmental toxicity.

The CERHR convenes a scientific expert panel that meets in a public forum to review, discuss, and evaluate the scientific literature on the selected chemical. Public comment is invited prior to and during the meeting. The expert panel produces a report on the chemical's reproductive and developmental toxicities and provides its opinion of the degree to which exposure to the chemical is hazardous to humans. The panel also identifies areas of uncertainty and where additional data are needed. The CERHR expert panels use explicit guidelines to evaluate the scientific literature and prepare the expert panel reports. Expert panel reports are made public and comments are solicited.

Next, the CERHR prepares the NTP-CERHR report. The NTP-CERHR report includes the NTP brief on the chemical evaluated, the expert panel report, and all public comments. The goal of the NTP brief is to provide the public, as well as government health, regulatory, and research agencies, with the NTP's interpretation of the potential for the chemical to adversely affect human reproductive health or children's health. The NTP-CERHR report is made publicly available electronically on the CERHR web site and in hard copy or CD-ROM from the CERHR.

[1] Information about the CERHR is available on its web site (http://cerhr.niehs.nih.gov) or by contacting the director (P.O. Box 12233, MD EC-32, NIEHS, Research Triangle Park, NC 27709; telephone 919-541-3455; facsimile 919-316-4511; e-mail shelby@niehs.nih.gov). Information about the NTP is available on the web at http://ntp-server.niehs.nih.gov or by contacting the NTP Office of Liaison and Scientific Review at the NIEHS (liaison@starbase.niehs.nih.gov or 919-541-0530).

Introduction

In 1999, the CERHR Core Committee, an advisory committee composed of representatives from NTP member agencies, recommended seven phthalates for expert panel review. These chemicals were selected because (a) there is the potential for human exposure from their widespread use and occurrence within the environment, (b) they have a high production volume, (c) there is substantial scientific literature addressing the reproductive and/or developmental toxicities of these chemicals, and (d) they are of concern to the public. These seven phthalates are as follows:

- di(2-ethylhexyl)phthalate (DEHP)
- di-isononyl phthalate (DINP)
- di-isodecyl phthalate (DIDP)
- di-*n*-butyl phthalate (DBP)
- butyl benzyl phthalate (BBP)
- di-*n*-octyl phthalate (DnOP)
- di-*n*-hexyl phthalate (DnHP)

Phthalates are a group of similar chemicals widely used to soften and increase the flexibility of plastic consumer products such as shower curtains, medical devices, upholstery, raincoats, and soft squeeze toys. They are not bound to the plastics and can leach into the surrounding environment. DEHP has the greatest production volume of the selected phthalates (approximately 260 million pounds [1994]), followed by DIDP (approximately 240 million pounds [1994]), and DINP (approximately 215 million pounds [1994]). The scientific literature on the reproductive and developmental toxicities of several phthalates is extensive. In addition, there is widespread public concern about the safety of phthalates in Europe, Canada, and the United States.

As part of the evaluation of phthalates, the CERHR convened a panel of scientific experts (Appendix I) to review, discuss, and evaluate the scientific evidence on the potential reproductive and developmental toxicities of each phthalate. There were three public meetings of this panel (August 17-19 and December 15-17, 1999 and July 12-13, 2000). The CERHR received numerous public comments on the phthalates throughout the evaluation process.

The NTP has prepared an NTP-CERHR report for each phthalate. The report on DBP includes the NTP brief on DBP, a list of the expert panel members (Appendix I), the expert panel's report on DBP (Appendix II), and all public comments received on that report (Appendix III). The NTP-CERHR report is intended to serve as a single, collective source of information on the potential for DBP to adversely affect human reproduction or development. Those interested in reading this report may include individuals, public interest groups, and staff of health and regulatory agencies.

The NTP brief included within this report presents the NTP's interpretation of the potential for exposure to DBP to cause adverse reproductive or developmental effects in people. It is based upon information about DBP provided in the expert panel report, the public comments, and additional scientific information available since the expert panel meetings. The NTP brief is intended to provide readers with clear, balanced, scientifically sound information on the potential for DBP exposures to result in adverse health effects on development and reproduction.

NTP Brief on Di-n-butyl Phthalate (DBP)

What is DBP?

DBP is a clear, oily liquid with the chemical formula $C_{16}H_{22}O_4$ and the structure shown in Figure 1. It is one of a group of industrially important chemicals known as phthalates. Phthalates are used primarily as plasticizers to add flexibility to plastics. Unlike many phthalates, DBP is not currently used as a plasticizer in polyvinyl chloride (PVC) plastics. Typically, DBP is used as a component of latex adhesives. It is also used in cosmetics and other personal care products, as a plasticizer in cellulose plastics, and as a solvent for dyes.

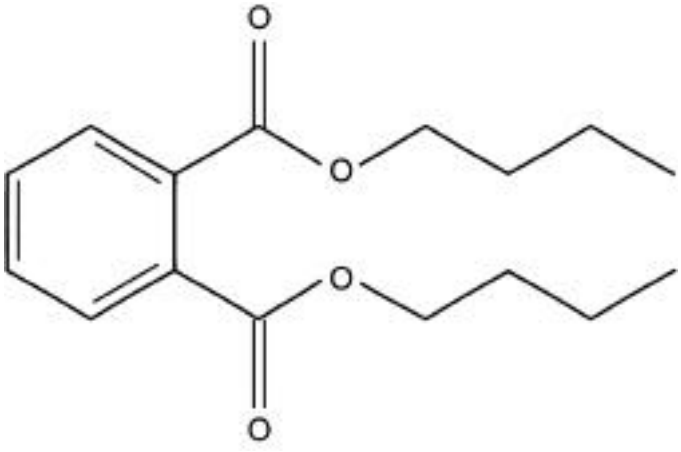
DBP is produced by reacting n-butanol with phthalic anhydride. The most recent information available indicates that approximately 7.7 million kilograms (17 million pounds) of DBP were produced in the United States in 1994 (ATSDR, 2001).

Are People Exposed to DBP?

Yes. There are several ways that people may be exposed to DBP at home or at work. Human exposure to DBP can occur during the manufacture of DBP, during the manufacture of DBP-containing products such as latex adhesives, during the use of such products, or through the presence of DBP in the environment.

Environmental exposures can occur through air, water, or food. Most people are exposed to DBP primarily through food. DBP migrates into foods, particularly fatty foods, from DBP-containing materials that are used to process and package food. Cosmetics and other personal care products may be another important source of exposure through inhalation or contact with the skin. Studies to determine the extent of such exposures have not been conducted.

Figure 1. Chemical structure of DBP



The expert panel estimated that the U.S. general population is exposed to approximately 2-10 µg/kg bw/day (micrograms per kilogram body weight per day). This reflects a total daily exposure of approximately 140-700 µg per person per day. By comparison, a small drop of water weighs approximately 30,000 µg and a grain of table salt weighs approximately 60 µg.

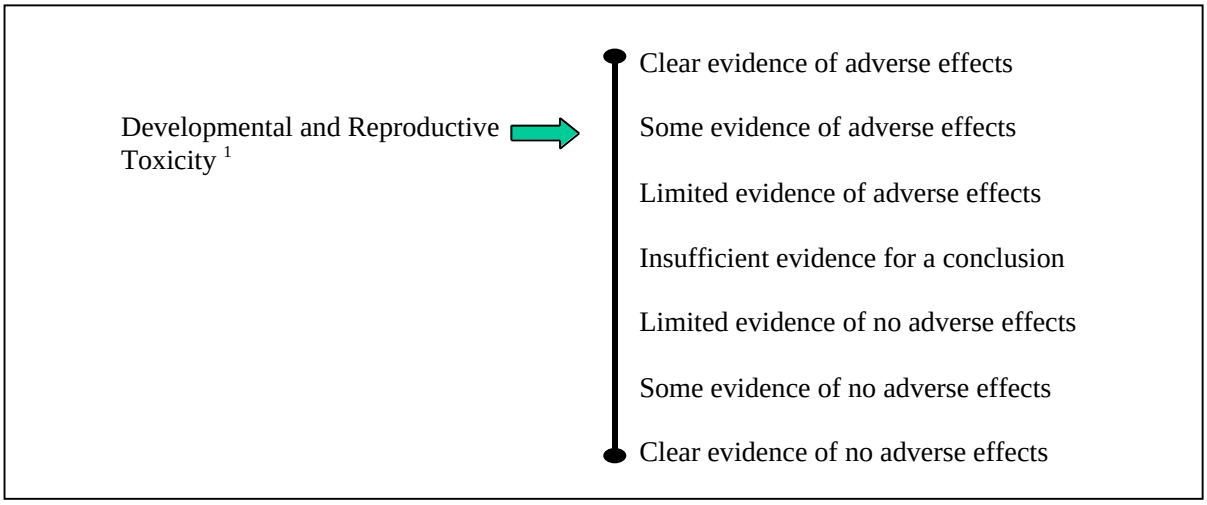
A recent study not available to the expert panel determined the amount of DBP metabolites in human urine (Blount et al., 2000). Kohn et al. (2000) used the data from that study to estimate daily exposure levels of DBP. They estimated that 95% of people are exposed to less than 10 µg DBP/kg bw/day, consistent with the expert panel's estimate. However, it was found that some women of reproductive age (20-40 years) are exposed to substantially higher DBP levels (over 100 µg/kg bw/day) than other age or sex groups. Neither the sources nor circumstances of these apparently higher exposures are known. It has been suggested that these higher exposures might be related to the use of DBP-containing personal care products such as perfumes, nail polishes, and hair spray (Blount et al., 2000).

Workers producing DBP can be exposed through skin contact or inhalation. It has been estimated that such exposures might be as high as 143 µg/kg bw/day, but are generally thought to be well below this level. Information is not available on exposure of workers who use DBP to manufacture other products.

Can DBP Affect Human Development or Reproduction?

Yes. Although there is no direct evidence that exposure of people to DBP adversely affects reproduction or development, studies with laboratory rodents show that exposure to DBP can cause adverse effects (Fig. 2). Based on recent data on the extent to which humans absorb, metabolize and excrete DBP, the NTP believes it is reasonable and prudent to conclude that the results reported in laboratory animals indicate a potential for similar or other adverse effects in human populations.

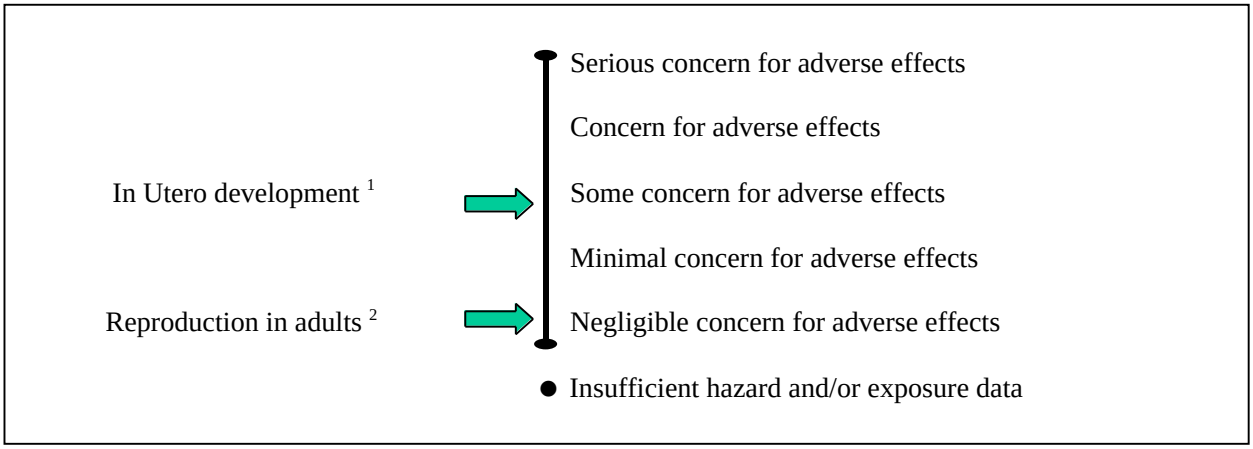
Figure 2. The weight of evidence that DBP is a developmental or reproductive toxicant



[1]Based on animal data only

Scientific decisions concerning health risks are generally based on what is known as "weight-of-the-evidence." In this case, recognizing the lack of human data and the level of evidence of effects in laboratory animals (Fig. 2), the NTP judges the scientific evidence sufficient to conclude that DBP may adversely affect human reproduction or development if the levels of exposure are sufficiently high.

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction may be adversely affected by exposure to DBP



[1]Maternal exposure to ~100 µg/kg bw /day (Kohn et al. estimated exposure)
[2] Exposure to 2-10 µg/kg bw/day

Summary of Supporting Evidence

As presented in the expert panel report, many of the DBP studies in rodents addressed both developmental and reproductive effects. These studies have reported that exposure of pregnant dams to relatively high doses of DBP causes reduced fetal survival and reduced birth weights among surviving offspring. In some instances, this exposure was also associated with skeletal malformations and abnormalities of the reproductive systems and organs in both male and female offspring. Exposure to DBP has also been shown to reduce fertility in female rats and mice. It is clear from studies with laboratory animals that rodents in prenatal and early postnatal stages of development are more sensitive to the reproductive effects of DBP than are adult animals. It is important to note that DBP exposure levels that lead to these adverse effects in rodents are generally far higher than those experienced by people.

The developing male reproductive system of rodents appears particularly sensitive to the adverse effects of DBP exposure. There is growing evidence that this male sensitivity may result from an antiandrogenic effect (reduced testosterone) of DBP. In a recent study, Shono et al. (2000) showed that exposure to the monoester metabolite of DBP, monobutyl phthalate (MBP), is toxic to the male reproductive tract. Pregnant dams were given an oral dose of 300 mg/day of MBP on various days during pregnancy; fetuses were obtained by Caesarean section.

On gestation day 20. Significant inhibition of testis migration was reported for male fetuses exposed to MBP on gestation days 11-14 and 15-18, with the greatest inhibition observed in the latter group. There were also treatment-related effects on the male reproductive tract along with a reduction in testicular testosterone levels. This study supports the role of MBP in mediating DBP toxicity to the male reproductive tract.

A report by Foster et al. (2000) proposes that the use of rat data to assess human risks for reproductive or developmental effects may be inappropriate because humans might be much less efficient at producing the active DBP metabolite, MBP. However, a recent study (Anderson et al., 2001) supports using DBP rodent data for evaluating potential effects in humans. It offers evidence that people efficiently absorb and metabolize DBP. The results show that human volunteers given an oral dose of DBP excrete approximately 70% of it as MBP in urine after 24 hours.

Are Current Exposures to DBP High Enough to Cause Concern?

Probably. More data are needed to better understand human DBP exposure levels and how these exposures vary across the population. Although the general U.S. population presently appears to be exposed to DBP at levels that are not of immediate concern for causing adverse reproductive or developmental effects, data are not available to permit conclusions regarding the possibility of effects in various age groups, occupations, or socioeconomic strata. Thus, the NTP offers the following conclusions.

Based upon recent estimated DBP exposures among women of reproductive age, the NTP has some concern for DBP causing adverse effects to human development, particularly development of the reproductive system.

This level of concern is greater than that expressed by the Phthalates Expert Panel and is based on recent exposure estimates that were not available to the expert panel.

Based upon current estimated exposure of the general population to DBP, the NTP concurs with the CERHR Phthalates Expert Panel that there is negligible concern for reproductive toxicity in exposed adults.

However, further data and evaluation are needed to determine if the higher DBP exposure levels reported for some women of reproductive age justify a higher level of concern for effects on their reproductive system.

References:

Anderson WAC, Castle L, Scotter MJ, Massey RC, Springall C. A biomarker approach to measuring human dietary exposure to certain phthalate diesters. Food Additives & Contaminants18:1068-1074 (2001).

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Blount BC, Silva MJ, Caudill SP, Needham LL, Pirkle JL, Sampson EJ, Lucier GW, Jackson RJ, Brock JW. Levels of seven urinary phthalate metabolites in a human reference population. Environmental Health Perspectives 108: 979-982 (2000).

Foster PMD, Cattley RC, Mylchreest E. Effects of di-*n*-butyl phthalate (DBP) on male reproductive development in the rat:Implications for human risk assessment. Food and Chemical Toxicology, 2000, 38, S97-S99.

Kohn MC, Parham F, Masten SA, Portier CJ, Shelby MD, Brock JW, Needham LL. Human exposure estimates for phthalates. Environmental Health Perspectives 108: A440-A442 (2000).

Shono T, Kai H, Suita S, Nawata H Time-specific effects of mono-*n*- butyl phthalate on the transabdominal descent of the testis in rat fetuses. BJU International 86, 121-125 (2000).

Appendix I. NTP-CERHR Phthalates Expert Panel Report on DBP

A 16-member panel of scientists covering disciplines such as toxicology, epidemiology, and medicine was recommended by the Core Committee and approved by the Associate Director of the National Toxicology Program. Over the course of a 16-month period, the panel critically reviewed more than 500 documents on 7 phthalates and identified key studies and issues for plenary discussions. At three public meetings[2], the expert panel discussed these studies, the adequacy of available data, and identified data needed to improve future assessments. At the final meeting, the expert panel reached conclusions on whether estimated exposures may result in adverse effects on human reproduction or development. Panel assessments were based on the scientific evidence available at the time of the final meeting. The expert panel reports were made available for public comment on October 10, 2000, and the deadline for public comments was December 11, 2000 (*Federal Register* 65:196 [10 Oct. 2000] p60206). The Phthalates Expert Panel Report on DBP is provided in Appendix II and the public comments received on that report are in Appendix III. Input from the public and interested groups throughout the panel's deliberations was invaluable in helping to assure completeness and accuracy of the reports. The Phthalates Expert Panel Reports are also available on the CERHR website (http://cerhr.niehs.nih.gov).

[2] Phthalate Expert Panel meeting dates were: August 17-19, 1999, in Alexandria, VA; December 15-17, 1999, in Research Triangle Park, NC; and July 12-13, 2000, in Arlington, VA.

Appendix I. NTP-CERHR Phthalates Expert Panel

Name	Affiliation
Robert Kavlock, Ph.D. (**Chair**)	EPA/ORD, Research Triangle Park, NC
Kim Boekelheide, M.D., Ph.D.	Brown University, Providence, RI
Robert Chapin, Ph.D.	NIEHS, Research Triangle Park, NC
Michael Cunningham, Ph.D.	NIEHS, Research Triangle Park, NC
Elaine Faustman, Ph.D.	University of Washington, Seattle, WA
Paul Foster, Ph.D.	Chemical Industry Institute of Toxicology, Research Triangle Park, NC
Mari Golub, Ph.D	Cal/EPA, Davis, CA
Rogene Henderson, Ph.D.	Inhalation Toxicology Research Institute, Albuquerque, NM
Irwin Hinberg, Ph.D.	Health Canada, Ottawa, Ontario, Canada
Ruth Little, Sc.D.	NIEHS, Research Triangle Park, NC
Jennifer Seed, Ph.D.	EPA/OPPT, Washington, DC
Katherine Shea, M.D.	North Carolina State University, Raleigh, NC
Sonia Tabacova, M.D., D. Sc.	FDA, Rockville, MD
Rochelle Tyl, Ph.D.	Research Triangle Institute, Research Triangle Park, NC
Paige Williams, Ph.D	Harvard University, Cambridge, MA
Tim Zacharewski, Ph.D.	Michigan State University, East Lansing, MI

Appendix II. Phthalates Expert Panel Report on DBP (CD-ROM attached)

Appendix III. Public Comments on the Phthalates Expert Panel Report on DBP